Medical Staff Conference

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Inappropriate Antidiuretic Hormone Secretion

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Our patient this morning presented with an interesting metabolic problem which seems to represent a rare complication of drug therapy. The syndrome of inappropriate secretion of antidiuretic hormone (STADH) was first described in 1957 and has subsequently been found in association with a wide variety of disorders. It is an important syndrome to recognize since its treatment is usually simple and effective and also because it may represent the first manifestation of a serious underlying disorder.*

The case summary will be presented by Dr. Michael Jensen, following which the discussion of this problem will be led by Dr. Morris Schambelan from the Endocrine Division of the San Francisco General Hospital.

DR. JENSEN:† The patient is a 74-year-old white woman who was admitted on an emergency basis because of the acute onset of a confusional state. The patient was transferred from another hospital where she had been admitted for one week for evaluation of chronic complaints of indigestion associated with some nausea and vomiting. Upon admission to the hospital, serum electrolyte content was normal. Results of a complete gastrointestinal evaluation, including x-ray studies of the gallbladder and upper gastrointestinal tract and a barium enema, were within normal limits. Administration of amitriptyline was started, 100 mg daily, for depression and it was given for approximately six days. At that time, the patient became confused and lethargic and was transferred to the University of California Medical Center for further care, with no specific diagnosis being apparent.

The history was one of general good health except for chronic degenerative arthritis involving both hands and requiring intermittent indomethacin therapy.

On physical examination, the patient was seen to be very lethargic and somewhat confused. Blood pressure was 175/90 mm of mercury, pulse rate 96 beats per minute and regular, respiratory rate 14 per minute. A general physical examination failed to show any abnormalities but the neurological examination gave abnormal results in that the patient was disoriented as to time and place. There were no focal neurological signs.

On admission, hemoglobin was 14.1 grams per 100 ml, hematocrit 39.4 percent, leukocyte count 12,800 with 83 percent neutrophils, 8 percent lymphocytes and 9 percent eosinophils. Platelet count was 305,000 per cu mm, serum B_{12} level 1,020 pg, sedimentation rate 4 and prothrombin time 10.4 seconds. Electrolytes were decidedly abnormal; serum sodium was 99, potassium 3.6, chloride 66, bicarbonate 25 mEq per liter. Cal-

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cium was 9.1 mg per 100 ml, magnesium 1.8 mg per 100 ml and osmolality 208 mOsm per kg. Phosphorus was 2.3, glucose 103, creatinine .7, uric acid 2.3, blood urea nitrogen (BUN) 13 and total bilirubin 1.0 mg per 100 ml. Total protein 6.8 grams per 100 ml, globulin 2.7 grams per 100 ml, serum glutamic-oxaloacetic transaminase (SGOT) 25 IU per liter, amylase 291 IU per liter, triglycerides 61 mg per 100 ml, cholesterol 229 mg per 100 ml, tetraiodothyronine (T_4) 6.5 μg per 100 ml, T_4 iodine 4.2 mg per 100 ml and triiodothyronine (T_3) 32 percent. Urinalysis gave negative results, with a specific gravity of 1.005. A test of urine for porphyrins gave negative results. Spinal fluid protein was 47 grams per 100 ml, glucose 79 mg per 100 ml. Findings on electroencephalogram, brain scan and skull and chest x-ray studies were normal. A computerized tomographic brain scan showed a calcified pineal that was midline and also the presence of slightly atrophic ventricles. The electrocardiogram was abnormal due to a left anterior hemiblock.

Following admission to the hospital, it became rapidly apparent that the source of impaired consciousness was the severe electrolyte disturbance. The patient was treated with furosemide and isotonic replacement of urine volume and within a matter of three days the serum sodium level was up to 130 mEq per liter with a normalization of the rest of the electrolytes. As the electrolytes became normal, the patient became brighter. A search was made to determine the cause for the apparent inappropriate antidiuretic hormone (ADH) secretion. A complete neurological evaluation was done, as has already been reported.

The chest films did not show any suggestion of a pulmonary neoplasm. Similarly, results of radiographic studies of the gastrointestinal tract were within normal limits.

A very careful drug history revealed that the patient was taking only amitriptyline immediately before the onset of the hyponatremia syndrome. The amitriptyline was discontinued. During the hospital stay, the patient became brighter and oriented. At the time of discharge electrolytes remained normal on a free fluid intake.

DR. SCHAMBELAN:* I would like to begin this morning by reviewing some recent data regarding the normal control mechanisms for the secretion of antidiuretic hormone. With this background, I shall then examine the pathophysiology in this interesting syndrome in which secretion of the hormone is apparently inappropriate for the physiological setting (SIADH). I shall then turn to a consideration of the clinical situations in which SIADH occurs and pay particular attention to drug related causes, apparently the mechanism in the patient presented today.

The antidiuretic hormone in man is an octapeptide arginine vasopressin (AVP). It differs from the other major neurohypophyseal hormone, oxytocin, by virtue of the amino acid residues in the third and eighth positions. In other species, such as hogs, lysine replaces arginine at the eighth position. An intermediate peptide, arginine vasotocin, has been identified in the evolutionary scale and structurally represents a cross between AVP and oxytocin. These peptides are synethesized in the supraoptic and paraventricular nuclei and travel down their axons via the neurohypophyseal tract to the pars nervosa of the posterior pituitary where they are stored and secreted.

The major biological effect of vasopressin appears to be to decrease solute free water clearance by a direct action on the renal tubular epithelium. Hormone secretion is primarily responsive to change in body osmolality and the control mechanism is sufficiently sensitive to maintain osmolality within a 1 to 2 percent range. A precise feedback loop is operative in which a loss of water resulting in an increase in serum tonicity leads to antidiuretic hormone release, presumably mediated by osmoreceptors. Water retention results in dilution and return toward normal tonicity. A parallel mechanism in the hypothalamus involves a thirst center which is also stimulated by the increase in tonicity. Injection of hypertonic saline into the hypothalamus and direct electrical stimulation both result in drinking.

The recent availability of sensitive and specific radioimmunoassays for AVP have confirmed many of the earlier observations that were based on data derived during renal clearance studies or by less sensitive bioassay techniques. Husain et al[1] found low or unmeasurable AVP levels in water loaded subjects and in patients with pituitary diabetes insipidus, whereas, dehydration in normal subjects resulted in variable increases in AVP levels. The relationship between serum tonicity and AVP levels has been recently evaluated by Robertson et al[2] who made simultaneous measurements of plasma osmolality and plasma AVP levels in varying stages of hydration. AVP levels were low in water loaded

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normal subjects but began to increase sharply at approximately 285 mOsm per kg (Figure 1). It was noted that in patients with pituitary diabetes insipidus there occasionally would be measurable levels of AVP but that these were inappropriately low for the state of hyperosmolality. By contrast, elevated levels of AVP were noted in the several patients with nephrogenic diabetes insipidus that he studied.

In addition to an osmotic mechanism, AVP also responds to a variety of nonosmotic stimuli. A number of these such as standing, hemorrhage, application of tourniquets and states associated with a decrease in cardiac output can all be viewed as messages which relate a decrease in effective vascular volume. These stimuli can be so profound as to override osmotic control. This was shown in a recent study by Robertson[2] in which a water loaded normal subject with low or unmeasurable AVP levels had blood pressure lowered acutely with intravenous trimethaphan. Despite maintenance of the plasma osmolality at 280 mOsm per kg or below there was a sharp increase in the levels of AVP.

In addition to osmotic and volume factors, other stimuli for ADH release have been identified. A variety of drugs including nicotine, barbiturates and morphine can directly stimulate AVP release. Some recent studies have shown an increase to levels as high as 200 pg per ml after smoking two cigarettes; these levels are more than 20 times those seen during simple dehydration. A complex neural mechanism is also involved with stimuli such as stress, suckling and coitus resulting in enhanced secretion. Various manipulations of the adrenergic nervous system also exert effects upon the release of AVP.[3]

With this understanding of the physiological control mechanism for ADH one can examine the pathophysiology in SIADH. The first clear definition of such a syndrome was provided by Schwartz and Bartter[4] in their report of two patients with carcinoma of the lung who presented with hyponatremia. In a careful metabolic study they defined a relationship between the hyponatremia and the state of water balance. When fluid intake was increased from 2,000 to 3,000 ml per day the patients gained weight and went into positive fluid balance; sodium excretion increased and hyponatremia developed on the basis of dilution and net sodium loss. This resulted in a hypo-osmolar state and because simultaneously obtained urine osmolality ranged from 280 to 440 mOsm

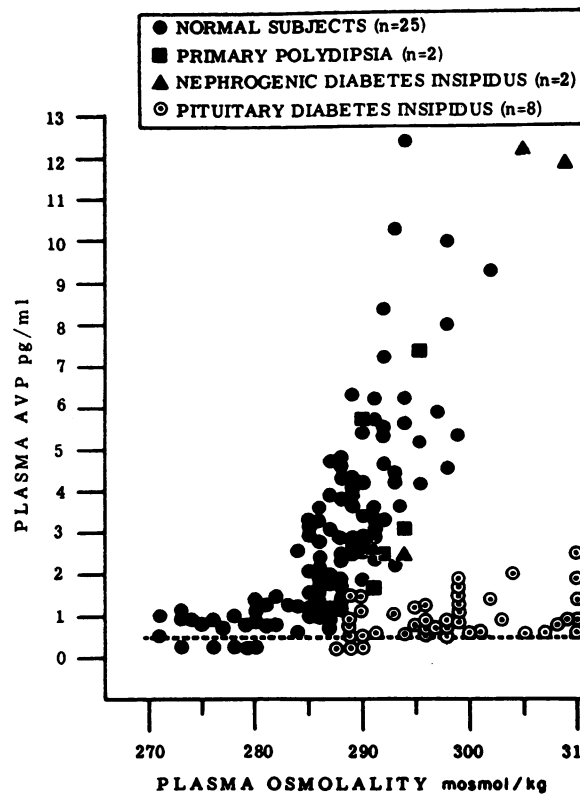

Figure 1.—The relationship of plasma arginine vasopressin (AVP) to plasma osmolality in normal subjects on varying fluid intakes and patients with polyuria of diverse causes. (Reproduced with permission from J Clin Invest[2])

per kg this was taken as *a priori* evidence for the presence of antidiuretic hormone.

In many respects their patients resembled the subjects studied by Leaf et al[5] several years earlier. In that study normal subjects were given exogenous vasopressin and developed hyponatremia only when allowed sufficient water intake to go into positive water balance. Natruresis occurred until a new steady state was reached. Administration of vasopressin to subjects on a restricted fluid intake did not result in these abnormalities. Subsequent studies in many other patients with the syndrome have showed the same characteristic relationship between fluid retention, natruresis and eventual development of hyponatremia and hypo-osmolality. In patients with the most severe hyponatremia, however, careful balance studies have not been able to account for the degree of hyponatremia solely on the basis of fluid retention and net sodium loss. It has been suggested that this discrepancy might be explained by osmotic inactivation of solutes.

The mechanism for the natruresis is also of in-

TABLE 1.—*Causes of Syndrome of Inappropriate Antidiuretic Hormone*

Malignancy
Lung
Pancreas
Duodenum
Thymoma
Central Nervous System
Meningitis
Trauma
Brain tumor
Brain abscess
Encephalitis
Guillain-Barré syndrome
Subarachnoid hemorrhage
Subdural hematoma
Acute intermittent porphyria
Central pontine myelinosis
Pulmonary
Pneumonia
Tuberculosis
Cavitation
Positive pressure respiration
Drugs
Vincristine
Chlorpropamide
Clofibrate
Carbamazepine
? Amitriptyline

terest. As a result of volume expansion there tends to be a slight increase in glomerular filtration rate in these patients, although this is not felt to be a sufficient explanation for the sodium wasting that occurs. In addition, volume expansion would presumably result in a decrease in renin and aldosterone secretion. When measured, aldosterone has frequently, but not invariably been subnormal in such patients. Furthermore, this syndrome can be produced experimentally in the face of replacement mineralocorticoids. It is currently presumed that a depression of proximal tubular sodium reabsorption, similar to the mechanism for natruresis in volume expanded animals, accounts for the natruresis in these patients ("third factor").

Recognition of the syndrome depends upon demonstration of hyponatremia and hypo-osmolality of body fluids with urine osmolality inappropriate to the state of hydration. This does not mean that the urine must be maximally concentrated; when steady state conditions are reached the urine osmolality is dependent upon the solute and water intake and may actually be lower than that in the plasma. It has been stressed that excretion of urine that is less than maximally dilute at a time when the body osmolality is subnormal is *a priori* evidence for the presence of antidiuretic hormone. Volume depletion and other nonosmotic stimuli must be excluded since, as we have seen, these can override the osmotic control of ADH. Similarly, the edematous states such as cirrhosis and congestive heart failure are frequently associated with elevated levels of ADH at a time when there is hypo-osmolality; in these patients there presumably is a decrease in effective vascular volume. Normal renal and adrenal function are prerequisites for the diagnosis of SIADH since patients with salt losing nephritis and Addison's disease can present with similar findings.

Other causes of hyponatremia may occasionally be confused with this syndrome, particularly in patients who have had solute loss in excess of water, either through extrarenal routes such as vomiting and diarrhea or via the kidney in patients receiving diuretics. While the fluid loss is usually hypotonic, the replacement is frequently more dilute (that is, water) leading to net hypotonic replacement and a dilutional hyponatremia. The stimulation to ADH may result in an increased urine osmolality, but unless there has been recent access to diuretics, the urinary sodium concentration is often low. This latter finding is also frequent in patients with edematous states who usually can be distinguished on clinical grounds as well. Other syndromes such as glucocorticoid insufficiency and myxedema can be almost indistinguishable from SIADH although in the latter case the mechanism is somewhat different.

The clinical situations that have been associated with SIADH are shown in Table 1. Malignant tumors, most commonly bronchogenic carcinoma, have been frequently reported in association with SIADH. There is now considerable evidence to suggest that such tumors are capable of secreting peptides which are either identical to or very similar to native antidiuretic hormone. A variety of central nervous system lesions have also been described in association with SIADH; presumably there is some interaction with the normal neural control of ADH release. The mechanism is less well understood in the nonmalignant pulmonary lesions although, in at least one patient with tuberculosis, there was evidence of a vasopressin like material in tuberculous lung tissue.[6]

The final category is of particular interest today because in the patient under discussion there may well have been a drug mechanism for the hyponatremia. The list of drugs associated with SIADH is steadily increasing and now includes such di-

verse agents as chlorpropamide, vincristine, clofibrate and carbamazepine. There is no reason to suspect that these drugs have identical mechanisms in causing this syndrome. For example, it appears that the occurrence of the syndrome in patients on vincristine may be restricted to those who have a toxic neuropathy from this drug. Recently increased levels of ADH were found in one such patient[7] and presumably there was some abnormality in the neural control of ADH release.

Perhaps the best studied of the agents has been chlorpropamide. A hyponatremic syndrome which is identical to SIADH can occur in patients receiving this drug and related sulfonylureas. While there is some suggestion that ADH levels may be slightly increased in such patients[8] the bulk of evidence suggests that the mechanism is due to an effect of chlorpropamide to enhance the action of vasopressin on the renal tubule. This is suggested by the fact that the drug has no action in rats with hereditary diabetes insipidus or patients with severe diabetes insipidus but does decrease water excretion in patients with mild pituitary diabetes insipidus. These observations suggest that small amounts of ADH are required for this effect. This is supported by recent studies in toad bladders which have shown a potentiation of the effect of vasopressin and theophylline by chlorpropamide. This direct renal effect is consistent with the observation that the drug has no effect in nephrogenic diabetes insipidus.

At this point we can return to the patient under discussion today. There seems little argument with the diagnosis of SIADH in view of the fact that in this patient there developed profound hyponatremia with associated weight gain, high urine osmolality and inappropriately high urinary sodium excretion with no evidence of dehydration or edema. Renal, thyroid and adrenal functions were subsequently shown to be normal. Proper consideration was given to exclude underlying causes such as occult malignancy or acute intermittent porphyria in view of the history of abdominal pain.

It is attractive to consider the possibility that the syndrome in this patient may have been related to amitriptyline in view of the fact that there has been a recent report of such a relationship.[9] Unfortunately, the patient today has been on other medications as well, although the syndrome clearly developed shortly after amitriptyline was added to the regimen. From an academic standpoint it would have been of interest to challenge the patient with this medication to see if the syndrome was reproducible but the clinicians wisely decided not to take this risk. At present the mechanism relating amitriptyline to SIADH is unknown.

We should close on a note about therapy in such patients. In mild cases simple water restriction will suffice. It is important to remember that some degree of negative sodium balance has occurred and the patient should be allowed access to salt as well. In very severe cases in which the hyponatremia is associated with coma or convulsions it may be necessary to raise the serum sodium rapidly. Administration of hypertonic saline has been the time honored approach. This is, however, potentially dangerous in patients with compromised cardiovascular systems and is only transiently effective since the salt load is rapidly excreted. The technique used in this patient in which furosemide is given in addition to hypertonic saline has recently been shown to be effective and, if proper monitoring conditions can be established, is perhaps the safest way to correct the hyponatremia rapidly.

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